

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 487/00	A2	(11) International Publication Number: WO 99/42465 (43) International Publication Date: 26 August 1999 (26.08.99)
(21) International Application Number: PCT/EP99/01013 (22) International Filing Date: 12 February 1999 (12.02.99) (30) Priority Data: 9803411.9 18 February 1998 (18.02.98) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BROMIDGE, Steven, Mark [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). SERAFINOWSKA, Halina, Teresa [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Harlow, Essex CM19 5AW (GB). (74) Agent: WATERS, David, Martin; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: NOVEL COMPOUNDS (57) Abstract Novel sulphonamide derivatives having CNS activity, processes for their preparation and their use as medicaments.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

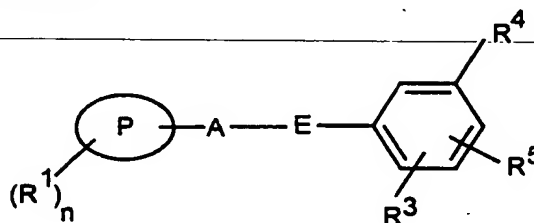
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

NOVEL COMPOUNDS

This invention relates to novel sulphonamide compounds having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of CNS disorders.

US patent 5,703,072 discloses bicyclic nonane and decane compounds having dopamine receptor affinity which are claimed to be of use in the treatment of schizophrenia. US patent 5,457,121 discloses cis-hexahydro-5-(1,2,3,4-Tetrahydro-2-naphthalenyl)pyrrolo<3,4,c>pyrroles as inhibitors of serotonin reuptake. European patent application EP 0815861 discloses a series of aryl sulphonamide compounds that are said to possess 5-HT₆ receptor activity and are useful in the treatment of various CNS disorders. A structurally distinct class of compounds has now been discovered, which have been found to have 5-HT₆ receptor antagonist activity.

The present invention therefore provides, in a first aspect, a compound of formula (I) or a salt thereof:



(I)

in which

E is -SO₂NH- or -NHSO₂-

P is a phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C₁₋₆alkylene or a C₁₋₆alkenylene group;

R¹ is halogen, C₁₋₆alkyl optionally substituted by one or more fluorine atoms, C₃₋₆cycloalkyl, C₁₋₆alkoxy, OCF₃, C₁₋₆alkoxyC₁₋₆alkoxy, C₁₋₆alkanoyl, amino, alkylamino or dialkylamino, SR¹¹ where R¹¹ is hydrogen or C₁₋₆alkyl or R¹ is phenyl, benzyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered

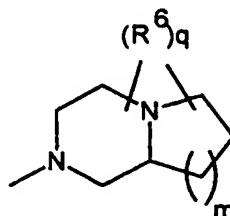
heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur; and

n is 0, 1, 2, 3, 4 or 5;

R³ is a group R⁵ or together with R⁵ forms a group (CH₂)₂O or (CH₂)₃O;

R⁴ is selected from a group of formula (i), (ii) or (iii):

Formula (i)

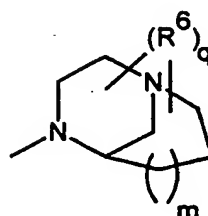


in which R⁶ is C₁-6alkyl optionally substituted by one or more halogen atoms;

5 m is 0, 1 or 2;

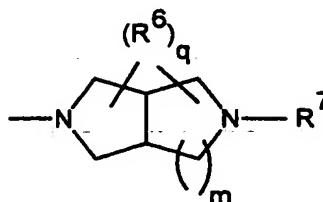
q is 0, 1, 2, 3 or 4; or

Formula (ii)



10 in which R⁶, m and q are as defined in formula (i); or

Formula (iii)



in which R⁶, and q are as defined in formula (I) and R⁷ is hydrogen or C₁-6alkyl;

15 R⁵ is hydrogen, halogen, C₁-6alkyl, C₁-6alkoxy optionally substituted with one or more fluorine atoms, trifluoromethyl, or together with R³ forms a group (CH₂)₂O or (CH₂)₃O.

20 Alkyl groups, whether alone or as part of another group, may be straight chain or branched. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

When the group P is a bicyclic heterocyclic ring suitable examples include benzothienyl, indolyl, quinolynyl or isoquinolynyl. When P is a 5 to 7-membered heterocyclic ring suitable examples include thienyl, furyl, pyrrolyl, triazolyl, diazoyl,

imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyrrolidinyl and pyrazinyl. The heterocyclic rings can be linked to the remainder of the molecule via any suitable carbon atom or, when present, a nitrogen.

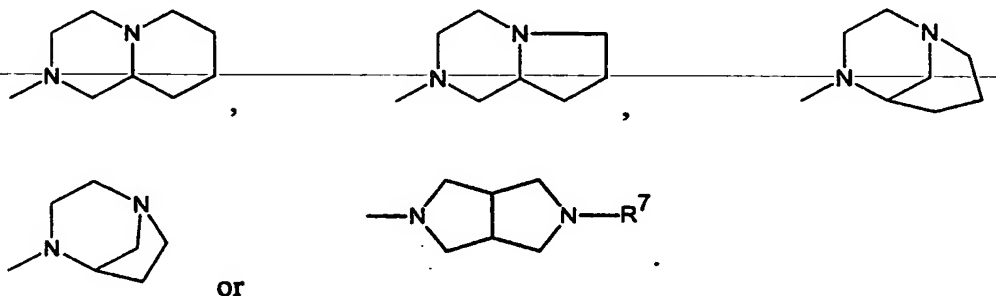
- 5 Preferably P is phenyl, naphthyl, thienyl and most preferably benzothienyl, Suitably A is a single bond, a methylene or ethylene group or a -CH=CH- group. Preferably A is a single bond or methylene.

- Suitably R¹ is hydrogen, halogen, phenyl, C₁₋₆alkoxy most preferably OMe, SR¹¹ most preferably SMe or C₁₋₆alkyl optionally substituted by one or more
10 fluorine atoms, for example methyl or trifluoromethyl. When R¹ is a heterocyclic group suitable examples include those listed above for P. Preferably n is 1, 2 or 3.

It will be appreciated that when R³/R⁵ groups are linked together the two groups must be attached to adjacent carbon atoms of the phenyl ring.

Preferably R³ is a group R⁵, in particular hydrogen.

- 15 Preferably R⁴ is a group:



Preferably R⁵ is C₁₋₆alkoxy, most preferably methoxy. Preferably R⁵ is para with respect to the sulphonamide linkage.

20

Particularly preferred compounds of the invention include

- 5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[4-methoxy-3-(octahydropyrido[1,2- α]pyrazin-2-yl) phenyl] amide,
S-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2-
25 α]pyrazine-2-yl)-4-methoxyphenyl],
R-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2- α]pyrazine-2-yl)-4-methoxyphenyl]amide,
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[3-(1,4-diazabicyclo-[3.3.1]non-4-yl)-4-methoxyphenyl]amide,
30 5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(1,4-diazabicyclo-[3.2.1]oct-4-yl)-4-methoxyphenyl]amide,

- 5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [4-methoxy-3-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)phenyl]amide,
 5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydropyrrolo-[3,4-*c*]pyrrol-2-yl)-4-methoxyphenyl]amide,
 5 N-(5-Bromo-3-fluoro-2-methoxyphenyl)-4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-*c*]pyrrol-2-yl]-benzenesulfonamide,
 and pharmaceutically acceptable salts thereof.

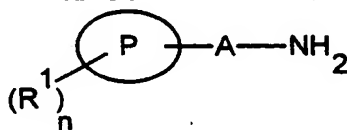
The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

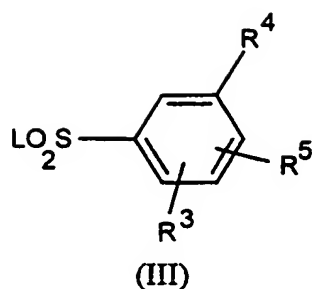
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including diastereomers and enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

- (a) when E is a group -NHSO_2^- , the coupling of a compound of formula (II):



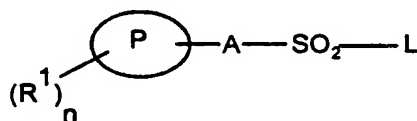
in which R^1 , P, n and A or protected derivatives thereof with a compound of formula (III):



in which R^3 , R^4 and R^5 are as defined in formula (I) and L is a leaving group; or

5

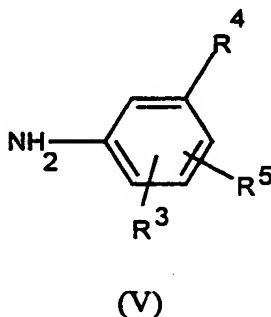
(b) when E is a group $-SO_2NH-$, the coupling of a compound of formula (IV):



10

(IV)

in which R^1 , P, n and A are defined in formula (I) and L is a leaving group with a compound of formula (V) or protected derivatives thereof:



15 in which R^3 , R^4 and R^5 are as defined for formula (I) and optionally thereafter:

- removing any protecting groups,
- forming a pharmaceutically acceptable salt.

20 Suitable leaving groups include halogen such as chloro or bromo, in particular chloro. The reactions of compounds of formula (II) and (III) and that of compounds of formula (IV) and (V) are typically carried out by mixing the two reagents together, optionally in an inert solvent such as dichloromethane or acetone. Such a reaction may be carried out in the presence of base.

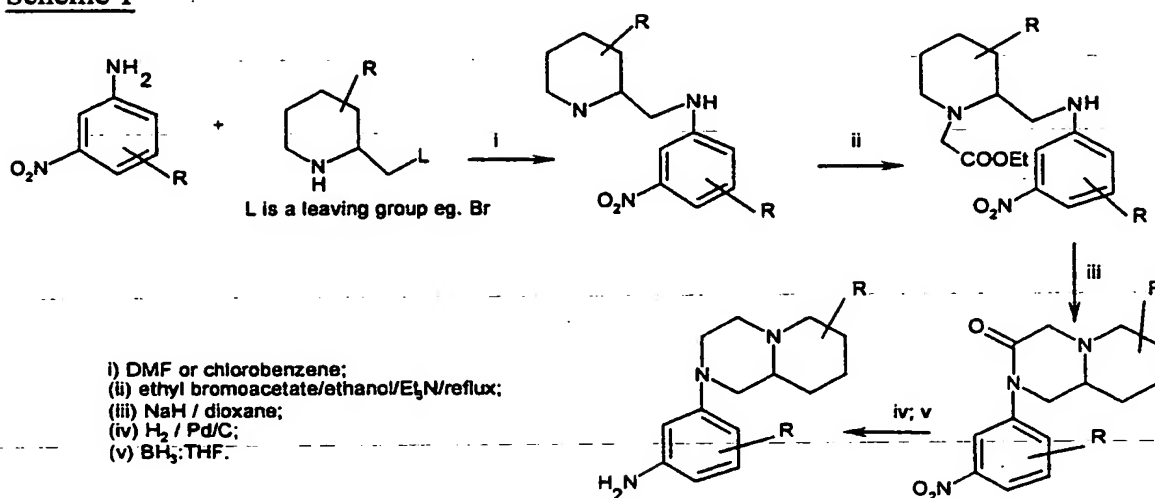
Those skilled in the art will appreciate that it may be necessary to protect certain groups. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981). For example, suitable protecting groups for the piperazine group include BOC, COCCl₃, COCF₃ and methyl the latter of which may be removed by treatment with 1-chloroethyl chloroformate according to standard procedures.

Compounds of formulae (II) to (IV) are commercially available or may be prepared according to known or analogous methods or following procedures described below. The procedures below are by way of illustration rather than limitation.

A compound of formula (III) (in which R⁴ is a group of formula (iii)), that is, 4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-*c*]pyrrolo-2-yl)-benzenesulfonyl chloride can be prepared by coupling *cis*-hexahydro-2-methylpyrrolo[3,4-*c*]pyrrole hydrochloride (US 5,457,121) with 2-bromoanisole using a palladium coupling reaction according to the general methodology disclosed by Buchwald (Tet. Lett. 1997, 38, 6359-6362). The resulting amine can be treated with chlorosulfonic acid in dichloromethane to give the required compound.

Aryl octahydropyrido[1,2-*a*]pyrazines of formula (V) (in which R⁴ is a group of formula (i)), can be obtained by a synthetic procedure as represented by scheme 1.

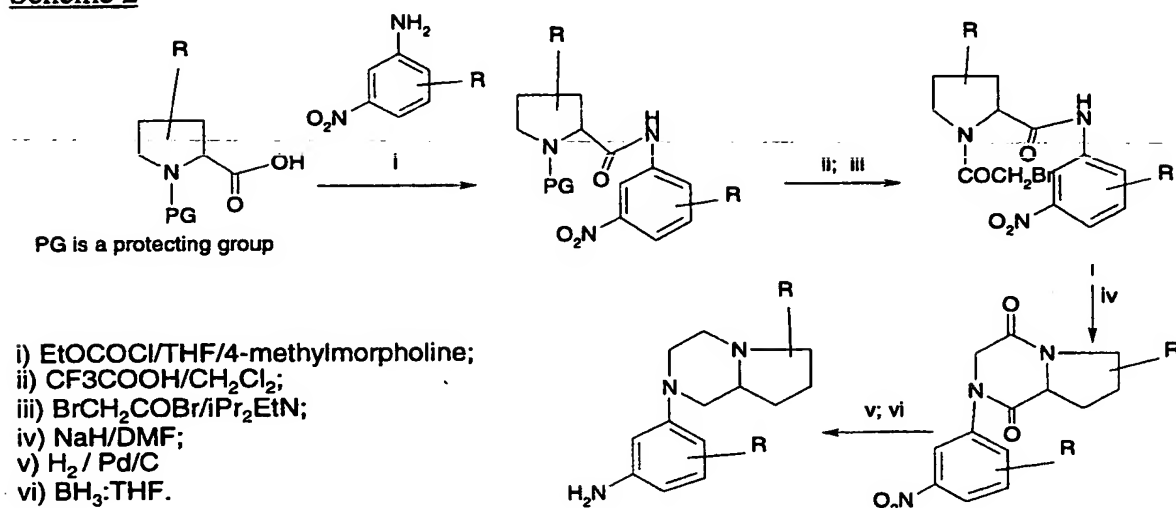
Scheme 1



Alternatively a modified strategy based on the use of a suitably protected proline derivatives can be used to prepare hexahydropyrrolo[1,2-*a*]pyrazines of general formula (V) using a synthetic procedure as represented by scheme 2. It is

noted that both enantiomers can be prepared starting from the appropriate chiral proline.

Scheme 2



5

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

- 10 Compounds of formula (I) and their pharmaceutically acceptable salts have 5HT₆ receptor antagonist activity and are believed to be of potential use in the treatment of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders e.g. Alzheimers disease, Parkinson' Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome),
- 15 sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

- 20 Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

- The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a
- 25 pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of the above disorders.

5 The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form
10 of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting
15 lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid
20 preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile
25 vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the
30 stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle.
35 Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

(2-Methoxy-5-nitrophenyl)piperidin-2-ylmethylamine (D1)

A mixture of 2-bromomethylpiperidine hydrobromide¹ (3.0 g, 11.6 mmol) and 2-methoxy-5-nitroaniline (34.8 mmol, 5.85 g) in chlorobenzene (100 mL) was heated under reflux for 17 h. The solvent was removed and the residue was dissolved in dichloromethane (100 mL), washed with 10% aqueous sodium hydroxide (3 x 20 mL) and dried (MgSO₄). The solvent was removed and the residue was purified by column chromatography on silica gel (eluting with dichloromethane-methanol gradient) to give the title compound (D1) as a dark green solid (1.45 g, 47%). MS: m/z (MH⁺) = 266.

1. T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, 24, 2485.

Description 2

{2-[(2-Methoxy-5-nitrophenylamino)methyl]piperidin-1-yl}acetic acid ethyl ester (D2)

A mixture of (2-methoxy-5-nitrophenyl)piperidin-2-ylmethylamine (D1) (0.27 g, 1 mmol), ethyl bromoacetate (0.15 mL, 1.35 mmol) and triethylamine (0.19 mL, 1.35 mmol) in dry ethanol (20 mL) was heated under reflux for 4 hours. The solvent was removed, the residue was dissolved in dichloromethane (70 mL), washed with aqueous sodium hydrogen carbonate (2 x 10 mL) and dried (MgSO₄). The solvent was removed and the residue was purified by column chromatography on silica gel

(eluting with dichloromethane-methanol gradient) to give the title compound (D2) as a tan gum (0.21 g, 60%). MS: m/z (MH⁺) = 352.

Description 3

5 2-(2-Methoxy-5-nitrophenyl)hexahydropyrido[1,2-*a*]pyrazin-3-one (D3)

A mixture of {2-[(2-methoxy-5-nitrophenylamino)methyl]piperidin-1-yl}acetic acid ethyl ester (D2) (0.3 g, 0.85 mmol) and sodium metal (20 mg, 0.87 mmol) in dry dioxane (8 mL) was heated under reflux for 40 minutes. The mixture was concentrated to a small volume, diluted with dichloromethane (50 mL), washed with
10 brine (2 x 10 mL) and dried (MgSO₄). The solvents were removed and the residue was purified by column chromatography on silica gel (eluting with dichloromethane-ethyl acetate gradient) to give the required product (D3) as a tan oil (0.08 g, 31%).
MS: m/z (MH⁺) = 306.

15 Description 4

2-(5-Amino-2-methoxyphenyl)hexahydropyrido[1,2-*a*]pyrazin-3-one (D4)

2-(2-Methoxy-5-nitrophenyl)hexahydropyrido[1,2-*a*]pyrazin-3-one (D3) (0.04 g) and Pd/C (0.05 g) in ethanol (15 mL) were stirred at room temperature under atmosphere of hydrogen for 4 hours. The catalyst was filtered off and washed with ethanol (2 x 15
20 mL). The filtrate and washings were combined and evaporated to dryness. The residue was co-evaporated with dry toluene (2 x 10 mL) to give the title compound (D4) as a colourless gum (0.035 g, 97%). MS: m/z (MH⁺) = 276.

Description 5

25 4-Methoxy-3-(octahydropyrido[1,2-*a*]pyrazin-2-yl)phenylamine (D5)

A solution of 2-(5-amino-2-methoxyphenyl)hexahydropyrido[1,2-*a*]pyrazin-3-one (D4) (0.035 g, 0.13 mmol) and borane-THF complex (1M solution, 1 mL) in tetrahydrofuran (5 mL) was heated under reflux for 4 hours. Dry methanol (2 mL) was added and the solvents were removed. The residue was redissolved in dry
30 methanol (5 mL) and cesium fluoride (0.035 g, 0.23 mmol) and dry potassium carbonate (0.035 g, 0.25 mmol) were added. The mixture was then heated under reflux for 5 hours. The solvent was removed, the residue was partially dissolved in dichloromethane (30 mL), washed with brine (3 x 10 mL), water (1 x 10 mL) and dried (MgSO₄). The solvent was removed to give the required product (D5) as a
35 slightly tan glass (0.03 g, 90%). MS: m/z (MH⁺) = 262.

Description 6

[N-(*tert*-Butoxycarbonyl)-L-prolinyl]-2-methoxy-5-nitrobenzeneamide (D6)

Ethyl chloroformate (1.3 mL, 14 mmol) was added dropwise to a solution of N-(*tert*-butoxycarbonyl)-L-proline (3.0 g, 14 mmol) and 4-methylmorpholine (1.54 mL, 14 mmol) in tetrahydrofuran (30 mL) at -10 °C. The resulting mixture was stirred at -10 °C for 10 minutes and 2-methoxy-5-nitroaniline (2.35g, 14 mmol) was added. The mixture was stirred at -10°C for 30 minutes and then at room temperature for 17 hours. The precipitate was removed by filtration and washed with tetrahydrofuran (3 x 20 mL). The filtrate and washings were combined and evaporated to dryness. The residue was dissolved in dichloromethane (100 mL), washed with aqueous sodium hydrogen carbonate (2 x 30 mL), dried (Na₂SO₄). The solvent was removed and the product was purified by column chromatography on silica gel (eluting with dichloromethane-ethyl acetate gradient) to give the title amide (D6) as a colourless glass (3.81 g, 75%). MS: m/z (MHNa⁺) = 389.

Description 7

15 S-Pyrrolidine-2-carboxylic acid (2-methoxy-5-nitrophenyl)amide (D7)

A solution of [N-(*tert*-butoxycarbonyl)-L-prolinyl]-2-methoxy-5-nitrobenzene-amide (D6) (1.8g, 4.93 mmol), trifluoroacetic acid (2.65 mL) and water (0.1 ml) in dichloromethane (15 mL) was stirred at room temperature for 17 hours. The solvents were removed and the residue was co-evaporated with toluene (2 x 40 mL). The resulting solid was dissolved in dichloromethane (200 mL) and washed with aqueous sodium hydrogen carbonate (2 x 50 mL). The aqueous layer was extracted with dichloromethane (4 x 50 mL), the combined extracts were dried (Na₂SO₄) and finally the solvent was removed to give the title compound (D7) as a cream solid (1.01 g, 77%). MS: m/z (MH⁺) = 266.

25

Description 8

S-1-Bromoacetylpyrrolidine-2-carboxylic acid (2-methoxy-5-nitro-phenyl)-amide (D8)

To a solution of S-pyrrolidine-2-carboxylic acid (2-methoxy-5-nitro-phenyl)-amide (D7) (0.2 g, 0.75 mmol) and N,N-diisopropylethylamine (0.13 mL, 0.75 mmol) in dichloromethane (10 mL) at -10°C was added dropwise bromoacetyl bromide (0.75 mmol, 0.07 mL) in dichloromethane (1 mL). The resulting reaction mixture was stirred at -10°C for 30 minutes and then at room temperature for 20 minutes. Subsequently, it was diluted with dichloromethane (50 mL), washed with aqueous sodium hydrogen carbonate (1 x 20 mL), water (1 x 20 mL) and dried (Na₂SO₄). The solvent was removed and the residue was co-evaporated with toluene (2 x 20 mL) to give the product (D8) (0.29 g) which was used without purification in the next step. MS: m/z (MH⁺) = 387.

Description 9**S-2-(2-Methoxy-5-nitrophenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D9)**

A mixture of S-1-bromoacetylpyrrolidine-2-carboxylic acid (2-methoxy-5-nitro-phenyl)amide (D8) (0.28 g, 0.7 mmol) and NaH (50 mg, 60% dispersion in mineral oil) in N,N-dimethylformamide (5 mL) was stirred at room temperature for 2 hours. A further amount of NaH was then added and the mixture was stirred at room temperature for additional 17 hours. The precipitate was filtered off and washed with dichloromethane (60 mL). The filtrate and washings were combined and evaporated to dryness. The residue was co-evaporated with toluene (2 x 10 mL). The product was purified by column chromatography on silica gel (eluting with dichloromethane-methanol gradient) to give the title compound (D9) as a colourless solid (0.079 g, 34% after two steps). MS: m/z (MH⁺) = 306.

15 Description 10**S-2-(5-Amino-2-methoxyphenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D10)**

A mixture of S-2-(2-methoxy-5-nitrophenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D9) (0.07 g) and Pd/C (0.08 g) in ethanol-ethyl acetate (8:2, 40 mL) was stirred at room temperature under atmosphere of hydrogen for 7.5 hours. The catalyst was filtered off, washed with ethanol (3 x 15 mL) and ethyl acetate (1 x 15 mL). The filtrate and washings were combined and evaporated to dryness. The product was purified by column chromatography (eluting with dichloromethane-methanol gradient) to give the title compound (D10) as a colourless solid (0.056 g, 89%). MS: m/z (MH⁺) = 276.

Description 11**S-3-(Hexahydropyrrolo[1,2-*a*]pyrazine-2-yl)-4-methoxyphenylamine (D11)**

A solution of S-2-(5-amino-2-methoxyphenyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (D10) (0.055 g, 0.2 mmol) and borane-THF complex (1M solution, 1.2 mL) in tetrahydrofuran (5 mL) was heated under reflux for 5 hours. A further amount of borane-THF complex (1M solution, 0.6 mL) was then added and the reaction was heated under reflux for another 2 hours. The solution was diluted with dry methanol (5 mL) and the solvents were removed. The residue was co-evaporated with dry benzene (2 x 5 mL) and redissolved in dry methanol (5 mL). Cesium fluoride (0.8 mmol, 0.12g) and dry potassium carbonate (0.87 mmol, 0.12 g) were added to the solution and the mixture was heated under reflux for 17 hours. A further amount of methanol (5 mL), cesium fluoride (0.8 mmol, 0.12g) and dry potassium carbonate

(0.87 mmol, 0.12 g) was then added and the reflux was continued for another 6 hours. Cesium fluoride (0.4 mmol, 0.06 g) and dry potassium carbonate (0.43 mmol, 0.06 g) were added again and the reflux was continued for 3 hours. The solvent was removed, the residue was partially dissolved in dichloromethane (50 mL), washed
5 with brine (3 x 20 mL), water (1 x 10 mL) and dried (Na₂SO₄). The solvent was removed to give the title compound (D11) as a tan gum (0.042 g, 85%). MS: m/z (MH⁺) = 248.

Description 12

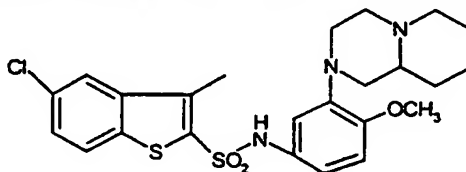
10 2-(2-Methoxyphenyl)-5-methyl-*cis*-octahydropyrrolo[3,4-*c*]pyrrole (D12)

A suspension of cesium carbonate (15g, 46mmol), palladium (II) acetate (0.15g, 0.7mmol) and 2,2'-bis(diphenylphosphine)-1,1'-binaphthyl (0.63g, 1mmol) in dry 1,4-dioxan (50ml) was degassed, purged with argon and sonicated for 10 minutes. 2-Bromoanisole (3.3ml, 27mmol) and *cis*-hexahydro-2-methylpyrrolo[3,4-*c*]pyrrole
15 hydrochloride [US 5,457,121 (1995)](1.9g) were added and the whole was again degassed, purged with argon and sonicated for 10 minutes. The stirred mixture was then refluxed under argon for 20 hours. The mixture was partitioned between dichloromethane (200ml) and 1M sodium hydroxide solution (100ml). The aqueous
layer was further extracted with dichloromethane (50ml) and the combined organic
20 extracts were dried (MgSO₄) and concentrated *in vacuo* to an oil. The oil was purified by column chromatography on silica gel eluting with a gradient of dichloromethane/methanol to afford the title compound (D12) as a solid (1.2g, 56%).
¹H NMR (CDCl₃, 250MHz) 2.34 (3H, s), 2.43-2.48 (2H, m), 2.62-2.69 (2H, m), 2.85-2.92 (2H, m), 2.99-3.04 (2H, m), 3.34-3.41 (2H, m), 3.85 (3H, s), 6.80-6.94 (4H, m);
25 (MH⁺) 232.

Description 13

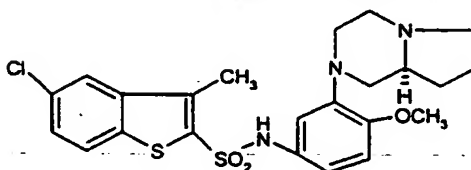
4-Methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-*c*]pyrrol-2-yl)-benzenesulfonyl chloride (D13)

30 A solution of 2-(2-methoxyphenyl)-5-methyl-*cis*-octahydropyrrolo[3,4-*c*]pyrrole (D12) (0.5g, 2.2mmol) in dry dichloromethane (3ml) was added over 5 minutes to ice cooled chorosulfonic acid (3ml) under argon. After stirring at 0°C for 0.25 hours and subsequently at room temperature for 1 hour, the solution was slowly poured onto a stirred mixture of ice (50g) and dichloromethane (50ml). The mixture was basified by
35 addition of excess saturated solution of sodium carbonate and the layers were separated. The aqueous layer was further extracted with dichloromethane (50ml) and the combined extracts were dried (MgSO₄) and concentrated *in vacuo* to give the title compound (D13) as a foam (0.25g 34%).

Example 1**5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid[4-methoxy-3-(octahydropyrido[1,2- α]pyrazin-2-yl) phenyl] amide (E1)**

5

A solution of 4-methoxy-3-(octahydropyrido[1,2- α]pyrazin-2-yl)phenylamine (D5) (0.03 g, 0.11 mmol), 5-chloro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.042 g, 0.15 mmol) and triethylamine (0.02 mL, 0.15 mmol) in dichloromethane (2 mL) was stirred at room temperature for 18 hours. The mixture was diluted with dichloromethane (20 mL), washed with saturated aqueous sodium hydrogen carbonate ((1 x 10 mL) and dried (MgSO₄). The solvent was removed and the product was purified by column chromatography on silica gel (eluting with dichloromethane-methanol gradient) to give the title compound (E1) as a cream solid (0.019 g, 32%). δ_H (250 MHz, CDCl₃), 1.28 (3H, m), 1.73 (3H, m), 2.08 (3H, m), 2.19 (3H, s), 2.43 (1H, m), 2.68 (1H, m), 2.84 (2H, m), 3.00 (1H, m), 3.21 (1H, m), 3.82 (3H, s), 6.46 (1H, d, J = 2.34 Hz), 6.73 (2H, m), 7.42 (1H, m), 7.65 (1H, d, J = 1.91 Hz), 7.72 (1H, d, J = 8.62 Hz). MS: m/z (MH⁺) = 506.

Example 2**5-Chloro-3-methylbenzo[b]thiophene-2-sulphonic acid [3-(hexahydropyrrolo[1,2- α]pyrazine-2-yl)-4-methoxyphenyl]amide (E2)**

A solution of 3-(hexahydropyrrolo[1,2- α]pyrazine-2-yl)-4-methoxy-phenylamine (D11) (0.04 g, 0.16 mmol), 5-chloro-3-methylbenzo[b]thiophene-2-sulphonyl chloride (0.045 g, 0.16 mmol) and pyridine (0.1 mL, 1.2 mmol) in dichloromethane (4 mL) was stirred at room temperature for 2 days. The mixture was diluted with dichloromethane (30 mL), washed with saturated aqueous sodium hydrogen carbonate (2 x 10 mL) and dried (Na₂SO₄). The solvent was removed and the product was purified by column chromatography on silica gel (eluting with dichloromethane-methanol gradient) to give the title compound (E2) as a pink glass (0.047 mg, 59%).

δ_H (250MHz, $CDCl_3$), 1.31 (1H, m), 1.82 (3H, m), 2.10 (3H, m), 2.22 (3H, s), 2.41 (1H, m), 2.60 (1H, m), 3.02 (1H, m), 3.17 (3H, m), 3.81 (3H, s), 6.51 (1H, d, $J = 2.08$ Hz), 6.70 (2H, m), 7.43 (1H, m), 7.66 (1H, d, $J = 1.90$ Hz), 7.74 (1H, d, $J = 8.60$ Hz). MS: m/z (MH^+) = 492.

5

Example 3**R-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2- α]pyrazine-2-yl)-4-methoxyphenyl]amide (E2)**

Following the same procedures as described for Example 2 the title compound (E3)

10 was prepared from N-(*tert*-butoxycarbonyl)-D-proline; 28% yield;

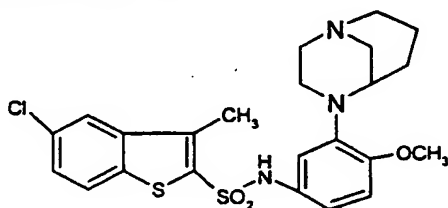
δ_H (250MHz, $CDCl_3$), 1.30 (1H, m), 1.81 (3H, m), 2.11 (3H, m), 2.22 (3H, s), 2.38 (1H, m), 2.60 (1H, m), 3.01 (1H, m), 3.18 (3H, m), 3.80 (3H, s), 6.50 (1H, d, $J = 2.16$ Hz), 6.70 (2H, m), 7.44 (1H, m), 7.66 (1H, d, $J = 1.90$ Hz), 7.74 (1H, d, $J = 8.60$ Hz). MS: m/z (MH^+) = 492.

15

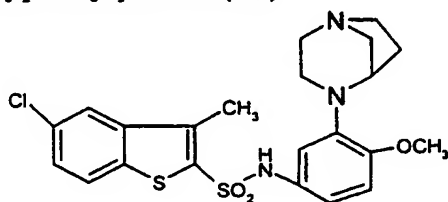
The following examples may be prepared by similar procedures to those described for Examples 1 and 2.

Example 4

20 **5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[3-(1,4-diazabicyclo-[3.3.1]non-4-yl)-4-methoxyphenyl]amide (E4)**

**Example 5**

25 **5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(1,4-diazabicyclo-[3.2.1]oct-4-yl)-4-methoxyphenyl]amide (E5)**

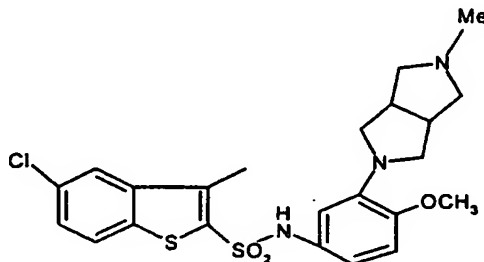


The following examples may be prepared by similar procedures to those described for
30 Example 1 employing the methodology described in US-5457121.

Example 6

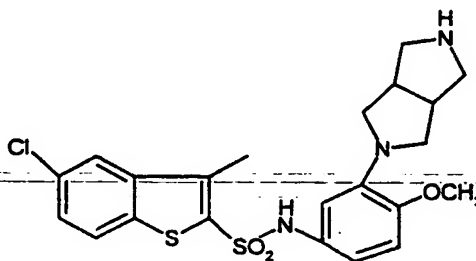
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [4-methoxy-3-(5-methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)phenyl]amide (E6)

5

**Example 7**

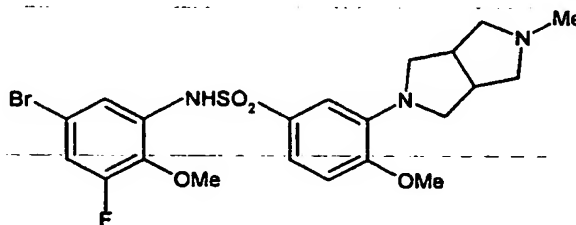
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydropyrrolo[3,4-*c*]pyrrol-2-yl)-4-methoxyphenyl]amide (E7)

10

**Example 8**

N-(5-Bromo-3-fluoro-2-methoxyphenyl)-4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-*c*]pyrrol-2-yl)-benzenesulfonamide hydrochloride (E8)

15



20 A solution of 5-bromo-3-fluoro-2-methoxy-aniline (160mg, 0.73mmol) and 4-methoxy-3-(5-methyl-*cis*-hexahydropyrrolo[3,4-*c*]pyrrol-2-yl)-benzenesulfonyl chloride (D13) (240mg, 0.73mmol) in dichloromethane (4ml) was stirred for 18 hours under argon. The solution was concentrated *in vacuo* and the residue was purified by

column chromatography eluting with a dichloromethane/methanol gradient to give the title compound (E8) as a foam (95mg, 24%); (MH⁺) 514/516.

5

Method for assay of 5-HT₆ antagonistic activity:

The test compounds were dissolved in polyethylene glycol:dimethyl sulphoxide (1:1) at 1 or 10mM and diluted to 0.1mM using 5mM tris buffer (pH 7.7 @ 25°C).

Dissolution was assisted by addition of 0.02ml 5M HCl plus heating to 40°C and

- 10 sonication for 10 minutes. Serial dilutions of test compounds in the same buffer were carried out using either a TECAN 5052 or Biomek 2000 Workstation. Samples of the diluted test compounds (0.05ml) were mixed with 0.05ml of radio-ligand [³H]-LSD prepared in the incubation buffer, and 0.4ml of a suspension of a preparation of the washed membranes of HeLa_5HT₆ cells (acquired from Dr. D. Sibley, NIH,
- 15 Bethesda, see Ref 1)(see Table 1), also in the incubation buffer. The details of the incubation conditions for each assay are shown in Table 2. The incubation buffer was 50mM Trizma (Sigma, UK) pH7.7 @ 25°C, 4mM MgCl₂.

After incubation at 37°C, the mixtures were filtered using a Packard Filtermate in

- 20 Packard TopCount format. Filters were washed with 4 x 1ml aliquots of ice-cold incubation buffer. Filters were dried and impregnated with 0.04ml of Microscint 20 (Packard). IC₅₀ values were estimated from the counts per minute using a four parameter logistic curve fit within EXCEL (2). K_i values were calculated using the method of Cheng and Prusoff (3). pIC₅₀ and pK_i are the negative log₁₀ of the molar IC₅₀ and K_i respectively.

25

Table 1 Details of the methods used to prepare membranes for binding assays

1st resuspension cells/ml	spin / resuspension 1, 2 ,3	Incubation before final spin	protein conc. in stored aliquots	cells /ml in stored aliquots
7 x 10 ⁷	Yes	20min at 37°C	4mg/ml	1.0 x 10 ⁸

Table 2 Summary of receptor binding assay conditions

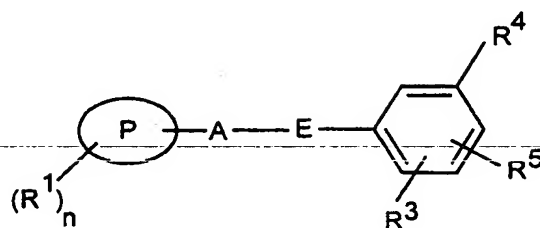
protein (ug/sample)	radio-ligand [³ H]-LSD (nM)	Specific Activity (Ci/mmol)	Non-Specific Definition	K _d (nM)
40	2.0	83	Methiothepin	3.1

References

1. MONSMA, F.J., SHEN, Y., WARD, R.P., HAMBLIN, M.W., SIBLEY, D.R..
1993. Cloning and expression of a novel serotonin receptor with high affinity for
5 tricyclic psychotropic drugs. *Mol. Pharmacol.*, **43**, 320-327.
2. BOWEN, W.P., JERMAN, J.C.. 1995. Nonlinear regression using spreadsheets.
Trends in Pharmacol. Sci., **16**, 413-417.
3. CHENG, Y.C., PRUSSOF, W.H.. 1973. Relationship between inhibition constant
(K_i) and the concentration of inhibitor which causes 50% inhibition (IC_{50}) of an
10 enzymatic reaction. *Biochem. Pharmacol.*, **92**, 881-894.

Claims:

1 A compound of formula (I) or a salt thereof:



(I)

in which

E is $-\text{SO}_2\text{NH}-$ or $-\text{NHSO}_2-$

P is a phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur;

A is a single bond, a C_{1-6} alkylene or a C_{1-6} alkenylene group;

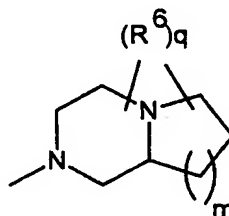
R^1 is halogen, C_{1-6} alkyl optionally substituted by one or more fluorine atoms, C_{3-6} cycloalkyl, C_{1-6} alkoxy, OCF_3 , C_{1-6} alkoxy C_{1-6} alkoxy, C_{1-6} alkanoyl, amino, alkylamino or dialkylamino, SR^{11} where R^{11} is hydrogen or C_{1-6} alkyl or R^1 is phenyl, benzyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur; and

n is 0, 1, 2, 3, 4 or 5;

R^3 is a group R^5 or together with R^5 forms a group $(\text{CH}_2)_2\text{O}$ or $(\text{CH}_2)_3\text{O}$;

R^4 is selected from a group of formula (i), (ii) or (iii)

Formula (i)

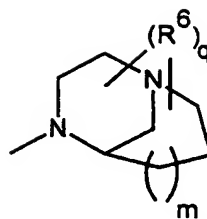


in which R^6 is C_{1-6} alkyl optionally substituted by one or more halogen atoms;

m is 0, 1 or 2;

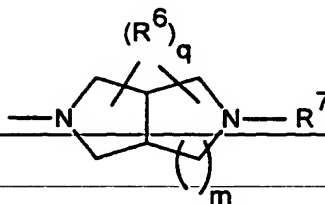
q is 0, 1, 2, 3 or 4; or

Formula (ii)



in which R^6 , m and q are as defined in formula (i); or

Formula (iii)



in which R^6 , m and q are as defined in formula (I) and R^7 is hydrogen or C_{1-6} alkyl; R^5 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy optionally substituted with one or more fluorine atoms, trifluoromethyl, or together with R^3 forms a group $(CH_2)_2O$ or $(CH_2)_3O$.

10

2. A compound according to claim 1 in which P is phenyl or benzothieryl.

15

3. A compound according to claims 1 and 2 in which A is a single bond.

4. A compound according to any one of claims 1 to 3 in which R^3 is hydrogen.

20

5. A compound according to any one of claims 1 to 4 in which R^5 is C_{1-6} alkoxy.

6. A compound according to any one of claims 1 to 5 in which R^5 is para with respect to the sulphonamide linkage.

25

7. A compound according to claim 1 which is:
5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[4-methoxy-3-(octahydropyrido[1,2- α]pyrazin-2-yl) phenyl] amide,
S-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2- α]pyrazine-2-yl)-4-methoxyphenyl],

- R-5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydro-pyrrolo[1,2- α]pyrazine-2-yl)-4-methoxyphenyl]amide,
 5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid[3-(1,4-diazabicyclo-
 [3.3.1]non-4-yl)-4-methoxyphenyl]amide,
 5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(1,4-diazabicyclo-
 [3.2.1]oct-4-yl)-4-methoxyphenyl]amide,
 5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [4-methoxy-3-(5-
 methylhexahydropyrrolo[3,4-*c*]pyrrol-2-yl)phenyl]amide,
 5-Chloro-3-methylbenzo[*b*]thiophene-2-sulphonic acid [3-(hexahydropyrrolo-[3,4-
c]pyrrol-2-yl)-4-methoxyphenyl]amide,
 N-(5-Bromo-3-fluoro-2-methoxyphenyl)-4-methoxy-3-(5-methyl-*cis*-
 hexahydropyrrolo[3,4-*c*]pyrrol-2-yl]-benzenesulfonamide
 and pharmaceutically acceptable salts thereof.

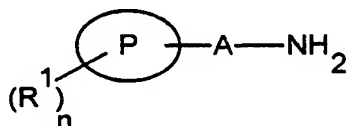
8. A compound according to any one of claims 1 to 7 for use in therapy.

9. A compound according to any one of claims 1 to 7 for use in the treatment of cognitive memory disorders, Parkinson's Disease, schizophrenia and/or depression.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.

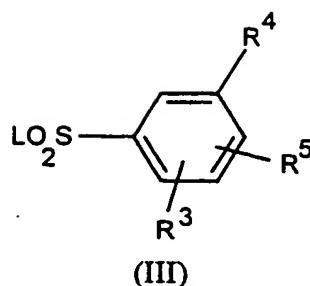
11. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

- (a) when E is a group -NHSO_2^- , the coupling of a compound of formula (II):



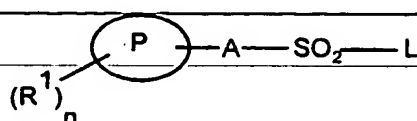
(II)

in which R^1 , P, n and A or protected derivatives thereof with a compound of formula (III):

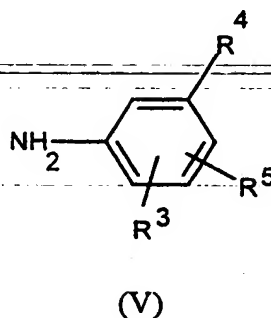


in which R^3 , R^4 and R^5 are as defined in formula (I) and L is a leaving group; or

- 5 (b) when E is a group $-\text{SO}_2\text{NH}-$, the coupling of a compound of formula (IV):



- 10 in which R^1 , P, n and A are defined in formula (I) and L is a leaving group with a compound of formula (V) or protected derivatives thereof:



in which R^3 , R^4 and R^5 are as defined for formula (I)

- 15 and optionally thereafter:

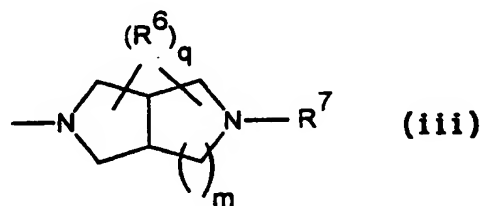
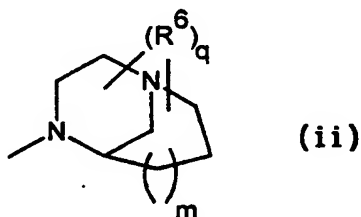
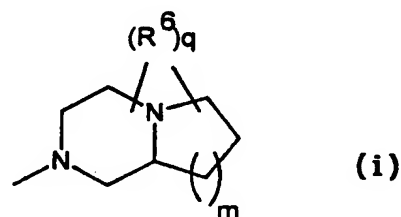
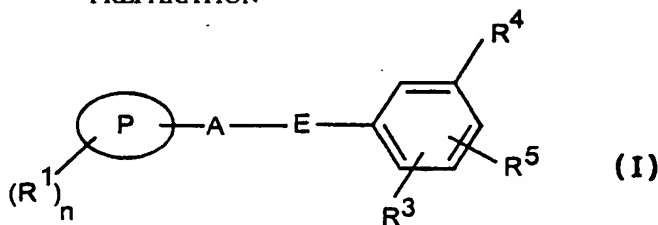
- removing any protecting groups,
- forming a pharmaceutically acceptable salt.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 487/08, A61K 31/495, C07D 333/68, 295/12 // (C07D 487/08, 333:00, 241:00), (C07D 487/08, 333:00, 209:00)		A3	(11) International Publication Number: WO 99/42465
			(43) International Publication Date: 26 August 1999 (26.08.99)
(21) International Application Number: PCT/EP99/01013			(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
(22) International Filing Date: 12 February 1999 (12.02.99)			
(30) Priority Data: 9803411.9 18 February 1998 (18.02.98) GB			
(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			
(72) Inventors; and (75) Inventors/Applicants (for US only): BROMIDGE, Steven, Mark [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). SERAFINOWSKA, Halina, Teresa [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Harlow, Essex CM19 5AW (GB).			
(74) Agent: WATERS, David, Martin; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).			Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
			(88) Date of publication of the international search report: 30 September 1999 (30.09.99)

(54) Title: SULPHONAMIDE DERIVATIVES BEING 5-HT₆ RECEPTOR ANTAGONISTS AND PROCESS FOR THEIR PREPARATION

**(57) Abstract**

Novel sulphonamide derivatives of formula (I) or a salt thereof having CNS activity, processes for their preparation and their use as medicaments: in which E is -SO₂NH- or -NHSO₂- P is a phenyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur; A is a single bond, a C₁₋₆alkylene or a C₁₋₆alkenylene group; R¹ is halogen, C₁₋₆alkyl optionally substituted by one or more fluorine atoms, C₃₋₆cycloalkyl, C₁₋₆alkoxy, OCF₃, C₁₋₆alkoxyC₁₋₆alkoxy; C₁₋₆alkanoyl, amino, alkylamino or dialkylamino, SR¹¹ where R¹¹ is hydrogen or C₁₋₆alkyl or R¹ is phenyl, benzyl, naphthyl, a bicyclic heterocyclic ring or is a 5 to 7-membered heterocyclic ring each containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulphur; and n is 0, 1, 2, 3, 4 or 5; R³ is a group R³ or together with R⁵ forms a group (CH₂)₂O or (CH₂)₃O; R⁴ is selected from a group of formula (i), (ii) or (iii): Formula (i) in which R⁶ is C₁₋₆alkyl optionally substituted by one or more halogen atoms; m is 0, 1 or 2; q is 0, 1, 2, 3 or 4; or Formula (ii) in which R⁶, m and q are as defined in formula (i); or Formula (iii) in which R⁶, and q are as defined in formula (i) and R⁷ is hydrogen or C₁₋₆alkyl; R⁵ is hydrogen, halogen, C₁₋₆alkoxy optionally substituted with one or more fluorine atoms, trifluoromethyl, or together with R³ forms a group (CH₂)₂O or (CH₂)₃O.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01013

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D487/08 A61K31/495 C07D333/68 C07D295/12
 //(C07D487/08,333:00,241:00),(C07D487/08,333:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 02502 A (MOSS STEPHEN FREDERIK ;BROMIDGE STEVEN MARK (GB); SMITHKLINE BEECH) 21 January 1999 see the whole document ---	1-11
P, X	WO 98 27081 A (BROMIDGE STEVEN MARK ;KING FRANCIS DAVID (GB); SMITHKLINE BEECHAM) 25 June 1998 see the whole document ---	1-11
X	EP 0 815 861 A (HOFFMANN LA ROCHE) 7 January 1998 see the whole document ---	1-11
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

15 July 1999

Date of mailing of the international search report

13.08.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01013

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SAUDOU F ET AL: "5-HT RECEPTOR SUBTYPES: MOLECULAR AND FUNCTIONAL DIVERSITY" MEDICINAL CHEMISTRY RESEARCH, vol. 4, no. 1, 1 January 1994, pages 16-84, XP000604196 * see page 18, fig.1 and pages 52/53 * see the whole document	1-11
Y	MONSMA ET AL: "Cloning and Expression of A Novel Serotonin Receptor with High Affinity for Tricyclic Psychotropic Drugs" MOLECULAR PHARMACOLOGY, vol. 43, no. 3, 1 January 1993, pages 320-327, XP002093842 see the whole document	1-11
Y	HOYER D AND MARTIN G: "5-HT receptor classification and nomenclature: towards a harmonization with the human genome" NEUROPHARMACOLOGY, no. 36, 1 April 1997, page 419 428 XP002075372 see the whole document	1-11
P,Y	WO 98 27058 A (WYMAN PAUL ADRIAN ;BROMIDGE STEVEN MARK (GB); KING FRANCIS DAVID ()) 25 June 1998 see the whole document	1-11
P,Y	BROMIDGE, S.M. ET AL.: "5-Chloro-N-(4-methoxy-3-piperazin-1-yl-phenyl)-3-methyl-2-benzothiophenesulfonamide (SB-271046): A Potent, Selective, and Orally Bioavailable 5-HT ₆ Receptor Antagonist" J.MED.CHEM., vol. 42, no. 2, 28 January 1999, pages 202-205, XP002109186 WASHINGTON see the whole document	1-11
P,Y	SLEIGHT ET AL: "The 5-hydroxytryptamine-6 receptor: localisation and function" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 8, no. 10, 1-October 1998, pages 1217-1224, XP002093843 see the whole document	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/01013

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Due to the fact that the claims 1 -5 encompass such an enormous amount of compounds which contain only a minor fixed part (structural isomerism, compare in particular the structural possibilities of the linking of P together with the linker groups A and E) and a large number of variables which themselves may contain variables (compare in particular formula (i), (ii) and (iii)), the scope of said claims cannot be evaluated and an exhaustive search is thus impossible. The search was limited to the compounds of claims 6 and 7 including claims 1-5 and 8-11 partially and to the general idea underlying the application. For these reasons a complete search has not been carried out (see Article 17 (b) PCT, Rule 33.3 and Guidelines III, 2.3).

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/EP 99/01013

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9902502	A	21-01-1999	AU 9257898 A	08-02-1999
WO 9827081	A	25-06-1998	AU 6090498 A	15-07-1998
EP 0815861	A	07-01-1998	AU 694696 B	23-07-1998
			AU 2841697 A	22-01-1998
			BR 9703788 A	17-11-1998
			CA 2209018 A	28-12-1997
			CN 1170574 A	21-01-1998
			CZ 9702002 A	14-01-1998
			HR 970349 A	30-04-1998
			HU 9701096 A	01-02-1999
			JP 10067734 A	10-03-1998
			NO 972983 A	29-12-1997
			PL 320822 A	05-01-1998
WO 9827058	A	25-06-1998	NONE	

THIS PAGE BLANK (USPTO)